Protocol Synopsis

Name of Sponsor: Korea Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: Samsca® Tablets		Protocol# 156-KOA-1201n
Protocol Title:	Post Marketing Surveillance Study of Safety and Efficacy of Samsca® Tablets under the "New Drug Re-Examination"	
Clinical Phase:	Post Marketing Surveillance	
Treatment Indication:	The treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) and etc.	
Objective(s):	The objective of this study is to evaluate following items in relation with use of Samsca® in normal medical practice; 1. Serious adverse event and adverse drug reaction profile 2. Unexpected adverse event/adverse drug reaction profile 3. Known adverse drug reaction profile 4. Non-serious adverse drug reaction profile 5. Other information related to the product safety and efficacy The hypothesis of this study is that Samsca® is safe and efficacious in the treatment.	

Trial Design:	This is a Post-Marketing Surveillance study of Samsca® tablets in accordance with Korean regulations on New Drug Re-examination (i.e. New Drug Re-examination Standards: MFDS Notification No. 2015-79 dated 30Oct2015). This study will be conducted in a prospective, single-arm, multi-center format. As this study is observational in nature, the patient's follow-up is not prescriptive in nature and must be left up to the judgment of the physician (investigator), within the period of observation set forth in the protocol. The protocol will be developed in accordance with the MFDS guideline. *MFDS : Ministry of Food and Drug Safety
Trial Population:	At least 3000 patients will be enrolled for surveillance to meet the local regulatory requirements. About 100~150 investigators across the country will be participating in this surveillance and the number of patients to be enrolled by each investigator will vary.

Inclusion/Exclusion Criteria:	**Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study : 1. Patients who have hyponatremia in euvolemic or hypervolemic states, defined as serum sodium level < 125 mEq/L or hyponatremia that is symptomatic and has resisted correction with fluid restriction 2. Patients who are prescribed Samsca® treatment as per investigator's medical judgment 3. Patients who gave written authorization to use their personal and health data 4. Patients starting Samsca® treatment after agreement is in place Investigators will refer to the product market authorization (label) for inclusion criteria. **Exclusion Criteria** Subjects presenting with any of the following will not be included in the study: 1. Patients who have been treated with Samsca® 2. Patients with known or suspected hypersensitivity to tolvaptan or to any ingredient of the drug 3. Patients requiring urgent intervention to raise serum sodium acutely. 4. Inability of the patient to sense or appropriately respond to thirst. 5. Hypovolemic hyponatremia 6. Concomitant use of strong CYP3A inhibitors 7. Anuric patients 8. Volume depletion patients

	9. Hypernatremia patients 10. Women who are pregnant or possibly pregnant and lactation 11. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption Investigators will refer to the product market authorization (label) for exclusion criteria.
Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	**Dose:** Samsca® (Tolvaptan spray dry powder) Tablets, 15mg & 30mg **Dosage regimen:** Samsca® is being used 15mg/day to 60mg/day as per approved marketing authorization (labeling). Do not administer Samsca® for more than 30 days to minimize the risk of liver injury . **Mode of administration:** P.O **Treatment period:** It should be based on the patient's clinical response. Refer to the package insert for the detailed information on prescription.
Safety Measure:	1. Adverse Events (AEs)/Adverse Drug Reactions(ADRs), Serious Adverse Events(SAEs)/ Serious Adverse Drug Reactions(SADRs), Unexpected Adverse Events(UAEs)/Unexpected Adverse Drug Reactions(UADRs) 2. Others: vital signs (blood pressure and pulse), height, weight ,BMI
Efficacy Measures:	1. The change of serum sodium level from baseline to end of treatment period or discharge for a given hyponatremia treatment: Efficacy measurement covers a maximum of 4 days. 2. Overall judgement Holistically judge it according to the judgement of serum sodium level and clinical symptoms: Effective, No effect, Worsen

Statistical Methods:	Safety analysis set includes all subjects who received Samsca® tablets at least once and followed up for the safety evaluation. Efficacy analysis set includes all subjects who received Samsca® tablets and efficacy evaluation data is available. In interim reports, the descriptive statistics for continuous variables and frequency (n) and percentage (%) for categorical variables will be presented in overall patients. In final report (Re-examination report), safety and efficacy measures will be summarized and analyzed in overall patients and by background factors. For continuous variables, the descriptive statistics will be presented, and the analysis will be performed using the analysis of covariance (ANCOVA) model with background as a factor and baseline serum sodium level as a covariate. For categorical variables, frequency (n) and percentage (%) will be presented, and the analysis will be performed using Chi-square test or Fisher's exact test between categories of background factors. Also, 95% confidence interval of incidence rate of adverse event will be described. Data for special population (i.e. pregnant women, elderly patients, patients with liver or renal disease) will be presented as well.
Estimated Duration of study	Planned study schedule as per local regulation is as below; 1. Regulatory approval on Samsca®: September 2011 2. Product launch date: December 2012 3. Study period: September 2011 – August 2017 4. Interim reports to MFDS: every 6 months for first 2 years, then annually thereafter. 5. Final report to MFDS: within 3 months of study completion

[Appendix]

Management and reporting of safety information

Collection period of safety information is after first use of Otsuka product until 2 days after discontinuation RESEARCHER shall submit to OTSUKA any SAFETY EVENT within the following timeline:

(a) Twenty-four (24) hours from RESEARCHER's receipt of SAFETY EVENT classified as serious adverse event and non-serious adverse event (defined below) or Product Quality Complaint (PQC) or Pregnancy;

(b) For all other safety information as defined above and not specified in (a), RESEARCHER shall send the line-listing to OTSUKA at the end of each study, or during the study upon OTSUKA's request.

Procedures for the collection, management and reporting of individual cases of safety information while the study is being conducted, and for the periodic and end of study reconciliation of serious/non-serious adverse events between PV database and study database, aligned with the current version of G-SOP-ALL-007. Safety data reconciliation will be conducted comparing the safety database and the clinical database when study report (annual report& re-examination report) is submitted. The detail of reconciliation including frequency will be described in the Data Management Plan (DMP).

Below is the definition of Safety information including Adverse Event(AE), Serious Adverse Event(SAE), Non-Serious Adverse Event(NSAE).

Safety information	Safety Information as below will be reported in accordance with the current Otsuka Global GxP/Pharmacovigilance Glossary. "Any information from any source containing information including - Adverse event or suspension thereof - Lack of efficacy - Overdose/incorrect dosage (accidental or intentional) - Abuse/misuse (e.g., patients sharing medication) – even without resulting adverse reaction - Accidental exposure (e.g., child takes parent's medication) - Medication error

	- Withdrawal reactions - Disease progression/exacerbation of existing disease - Drug-drug/Drug-food interactions - Exposure to drug during pregnancy, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure) - Exposure to drug during lactation (including uneventful) - Suspected counterfeit product - Suspected transfer of infectious disease/agent by the medicinal product concerned - Product Quality Complaint (PQC) with safety related/medically important information - Pediatric use (if not an approved use) - Occupational exposure - Off-label use
Adverse Event (AE)	Any untoward medicinal occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (Directive 2001/83/EC amended by Directive 2010/84/ EU). An adverse event can therefore be any unfavorable and unintended sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered causally related to the medicinal product.
Serious Adverse Event (SAE)	Any adverse drug experience/event occurring at any dose which - results in death, - is life-threatening, - requires inpatient hospitalization or prolonged of existing hospitalization, - results in persistent or significant disability or incapacity, - is a congenital anomaly/birth defect,

	- is medically significant Life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe. A medically significant event is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g. medical, surgical) to prevent one of the other outcomes listed in the definition above) might be considered serious as well, examples of such include, but not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; or convulsions that do not result in hospitalization; or development of drug dependency of drug abuse.
Non-serious Adverse Event	All Adverse Events that do not meet the definition of a Serious Adverse Event are considered Non-serious Adverse Events.